Identification of natural products with biliary toxicity

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Abstract

Biliary atresia (BA) is a rare hepatobiliary disease affecting newborn babies that occurs worldwide. It begin with fibrosis and obstruction of the extrahepatic bile duct (EHBD) and progresses within months to cirrhosis; the disease is invariably fatal in infancy without surgical biliary damage and, in many cases, liver transplant. The cause of BA is unknown although epidemiological data suggest that BA results from an in utero environmental insult that spares the mother, strongly suggesting a developmental window-ofsusceptibility for the fetus.

The Wells lab and collaborators recently reported proof-of-concept studies that a toxin could be the cause of BA. We isolated a novel isoflavonoid, biliatresone, that causes BA-like diseases in larval zebrafish and in the newborns of livestock and mice exposed during pregnancy. This compound is highly electrophilic with a reactive a-methylene ketone that appears necessary for toxicity. The only toxin reported to be associated with BA in humans, the epoxide metabolite of aflatoxin B1, differs structurally from biliatresone but notably is also a potent electrophile. The goal of this proposal is to use information from biliatresone studies to identify structurally similar highly electrophilic natural products and to test these compounds as well as aflatoxin B1 for neonatal biliary toxicity. We will use in vitro assays to test for direct cholangiocyte toxicity, and will treat pregnant mice to determine whether the selected compounds have fetal EHBD toxicity in vivo.

These experiments will provide new insight into potential toxic etiologies of BA, identifying common motifs, potential susceptibility factors, and promising classes of therapeutic and preventative agents. Successful completion of this study would lead to a larger application to study links between toxic compounds and human exposures.